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Br J Cancer. 1998 Aug;78(4):478-83

J Immunother Emphasis Tumor Immunol. 1996 Jul;19(4):245-56.

Hybridoma. 1986 Jul;5 Suppl 1:S117-23.

Med Oncol Tumor Pharmacother. 1986;3(3-4):141-6.

Hybridoma. 1986 Jul;5 Suppl 1:S163-70.

Hybridoma. 1986 Jul;5 Suppl 1:S151-61

Hybridoma. 1986 Jul;5 Suppl 1:S125-32.

Hybridoma. 1986 Jul;5 Suppl 1:S175-83.

Christopher Yaen
US Patent Office
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pancreatic cancer. Seminars

al.: Specific antigen:
d. Sci. USA 76:1438-1442,

al.: Inhibition of growth
nal antibody. Cancer Res.

nal antibodies inhibit human
cells. Proc. Natl. Acad.

: Phase I clinical trial of
inal tumors. Lancet

.: Effects of monoclonal
testinal adenocarcinoma.

Human anti-idiotype anti-
the immune response bene-
USA, in press.

HYBRIDOMA
Volume 5, Suppl. 1, 1986
Mary Ann Liebert, Inc., Publishers

Clinical Trial of Wistar Institute 17-1A Monoclonal Antibody in Patients with Advanced Gastrointestinal Adenocarcinoma: A Preliminary Report

HARLAND VERRILL, MARSHALL GOLDBERG, ROBERT ROSENBAUM, RODERICK ABBOTT, LISA SIMUNOVIC, ZENON STEPLEWSKI,[1] and HILARY KOPROWSKI [1]

ABSTRACT

Immunotherapy using monoclonal antibody 17-1A has been performed on 22 patients with metastatic gastrointestinal cancer. Criteria for treatment included objective evidence of advanced colon, gastric, or pancreatic cancer (positive CAT scan or x-rays, elevated tumor markers, and/or abnormal liver function tests). The tumor tissue was antigenically positive in all cases. Performance status ranged from 50 to 100%. No adverse reactions were noted.

Of the 22 cases treated, 4 (18%) have died, none have rapidly progressive disease, 4 (18%) have slowly progressive disease, 10 (45%) are considered stable with disease, and none are considered partial or complete responses. It is too early to classify the response in 4 cases.

In 6 of 8 patients where anti-idiotypic data was available, death or progressive disease was correlated to negative anti-idiotypic response, and clinical stability to a positive anti-idiotypic response.

In the patients considered to be stable, the percent change from pre-treatment serum 19-9 concentrations to current values ranged from -10% to +353%. In the patients who have died or have been classified as slowly progressive the serum 19-9 changes ranged from +13% to +707%.

INTRODUCTION

Recently Sears, Steplewski, and Koprowski reported that single infusions of murine monoclonal antibody 17-1A exerted a beneficial therapeutic effect in a portion of patients with

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advanced gastrointestinal malignancies (1). The arming of effector monocytes and macrophages with monoclonal antibody and subsequent tumor cell destruction has been described by Steplewski et al. (2). We began this study in August 1985 in order to confirm these findings, and eventually to extend them by the use of other modalities such as pre-treatment with gamma interferon or infusion of multiple antibodies. Since then, we have treated 22 patients with advanced colon (Dukes' D), stomach, and pancreatic cancer with single 17-1A infusions pre-mixed with effector cell-enriched plasma obtained by leukopheresis. We have followed these patients by radiographic techniques, serum tumor markers, anti-idiotypic antibody response, and clinical progress.

MATERIALS AND METHODS

Serum levels of CA 19-9 antigen were assayed with the Centocor CA 19-9 Kit obtained from both Abbott Laboratories in North Chicago, Illinois and Centocor in Malvern, Pennsylvania.

CEA assays were performed with an Abbott CEA-EIA Monoclonal Kit from Abbott Laboratories in North Chicago, Illinois.

The anti-idiotypic response assays were performed at The Wistar Institute in Philadelphia, Pennsylvania.

The liver function tests including serum AST (SGOT), ALT (SGPT), bilirubin and alkaline phosphatase were assayed on a SMAC analyzer using standard methodologies from Technicon Instruments Corporation in Tarrytown, New York.

The cell counts were performed on a model S880 from Coulter Electronics, Inc. Hialeah, Florida. A final count of between 5 and 10 billion mononuclear leukocytes in 500 ml was obtained.

The tissue was tested for the presence of 17-1A and GA 73-3 antigen by use of The Vectastain ABC Kit from Vector Laboratories in Burlingame, California. The intensity of the staining reaction was graded from negative to 4+. The percentage of tumor cells expressing the antigens were noted.

PATIENT SELECTION

Twenty-two patients with biopsy proven advanced gastrointestinal adenocarcinoma were selected for this clinical trial. The primary and metastatic sites are shown in Table 1. Six of the patients were female and 16 male. Their ages ranged from 47 to 73 yrs. In all cases the primary and/or the metastatic tissue demonstrated reactivity to the 17-1A and/or the 73-3 monoclonal antibody, see Table 2. All patients had a Karnofsky performance status of 50% or greater (with one exception). No patients showed evidence of renal dysfunction. All blood counts were near normal with granulocytes greater than 1500/mm3, platelets greater than 150,000/mm3, and hematocrit greater than 30%. There was no evidence of cardiac disease in any of the patients. No patients with brain metastasis were accepted. Pregnant or lactating women were excluded from this study. Patients with active infections, other serious illnesses, or psychiatric disorders were not accepted. None of the patients accepted were on steroids, aspirin, non-steroid anti-inflammatory drugs, hormones, or any other cancer therapy. All patients had evaluatable disease by routine diagnostic tests (CAT scan, x-ray, elevated tumor markers or abnormal liver function tests.) and had no previous therapy with murine immunoglobulins, see Table 3. All patients had at least a three month expected survival and were able to sign an informed consent.

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ANTIBODY

The preparation of murine MAb 1083-17-1A (IgG2a isotype) against human CRC has been described previously (3). Monoclonal antibody GA 73-3 which was used only for tissue staining was obtained from the Wistar Institute, Philadelphia, Pa. The lot numbers of the 17-1A antibody, prepared by Centocor in Malvern, Pa., were 03194, 03464, and 00575.

ANTIBODY ADMINISTRATION

A scratch approximately 3 cm long was made on the patients forearm and 20 ul of saline containing 2 mg of 17-1A antibody was placed onto the scratch. At 10 and again at 30 minutes the scratch was observed and reported as positive or negative.

The leukopheresis machine used was model #1012 from The Haemonetics Corporation in Braintree, Massachusetts. The procedure used was that of the manufacturer. The infusion procedure consisted of introducing 200 mg of the 17-1A monoclonal antibody into the bag containing 5 to 10 billion leukocytes, gently mixing the contents of the bag for about 10 seconds, allowing a one hour incubation period at room temperature, and reinfusing into the patient over 1-1.5 hours.

POSTANTIBODY MONITORING

The patient's vital signs, temperature, and physical condition were closely observed during antibody infusion and for the next 2 to 4 hours. Blood samples were obtained before treatment, 1 and 4 days post treatment, weekly post treatment for 8 weeks, and monthly thereafter. Aliquots of serum were prepared and frozen.

CRITERIA OF RESPONSE

Following are definitions used to classify patient responses:

Complete Response - disappearance of all demonstrable disease.
Partial Response - reduction by 50% or more in the size of a measurable lesion accompanied by no increase in the size of any other measurable lesions or appearance of new lesions.
Stable Response - no new lesions and less than 25% increase in size of any measurable lesion.
Slow Progression - appearance of new lesions and/or an increase of between 25 and 50% in size of previous measurable lesions.
Rapid Progression - appearance of new lesions accompanied by an increase in size of greater than 50% in any measurable lesion.

RESULTS

The primary and metastatic sites in the experimental subjects are shown in Table 1. Table 3 shows the pre-treatment serum 19-9

levels, which ranged from normal to 10,908 u/ml and CEA levels, which ranged from normal to 752 ng/ml. The date of treatment with 17-1A, any previous treatment, and the classification of each patient is shown in Table 4. Of the 22 patients, 4 (18%) have died, 4 (18%) are slowly progressive, 4 (18%) are too early to evaluate, and 10 (45%) are stable.

In all cases no immediate or delayed side effects were noted. Vital signs showed no change throughout the infusion. Table 5 shows that the pre-treatment performance status on the 4 patients who have expired ranged from 25 to 100%. No autopsies were performed, however in 3 of the 4, the cause of death was clearly related to tumor progression. In the fourth patient the cause of death was septecemia.

Table 6 shows the percent change in the serum 19-9 marker from pre-treatment to latest available data in each of the subjects. In the patients who are classified as stable the percent change ranged from -10% to +353%. In those who have died or have been classified as slowly progressive, the percent change ranged from +13% to +707%. Figure 1 shows two examples of serial serum 19-9 values. Patient WC is considered stable while SK is a slowly progressive patient.

In 6 of the 8 patients where anti-idiotypic data was available (Table 7) death or slowly progressive disease was accompanied by negative anti-idiotypic response (2 cases) and clinical stability by a positive anti-idiotypic response (4 cases).

DISCUSSION

Our experience with 17-1A antibody strongly supports the safety of this immunotherapeutic agent. None of our patients had a pre-treatment reactive skin test nor did any show immediate or long term side effects from the infusion.

The lack of any partial responses, as defined above, supports the contention that metastatic lesions large enough to be detected on CAT scan, are unlikely to be reduced in volume solely by treatment with 17-1A monoclonal antibody. Although 45% of the subjects are currently classified as stable, we can expect that some will deteriorate with longer observation times.

An important hypothesis is whether clinical response can be correlated to the anti-idiotypic response, in that stability corresponds to positive response and progression corresponds to a negative response. To date, six of eight patient responses are consistent with this notion.

It is our hope that future clinical trials incorporating pre-treatment with gamma-interferon, infusion with selected multiple antibodies, or both will improve our therapeutic results.

ACKNOWLEDGMENTS

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FIGURE 1

SERUM CA 19-9 RESULTS

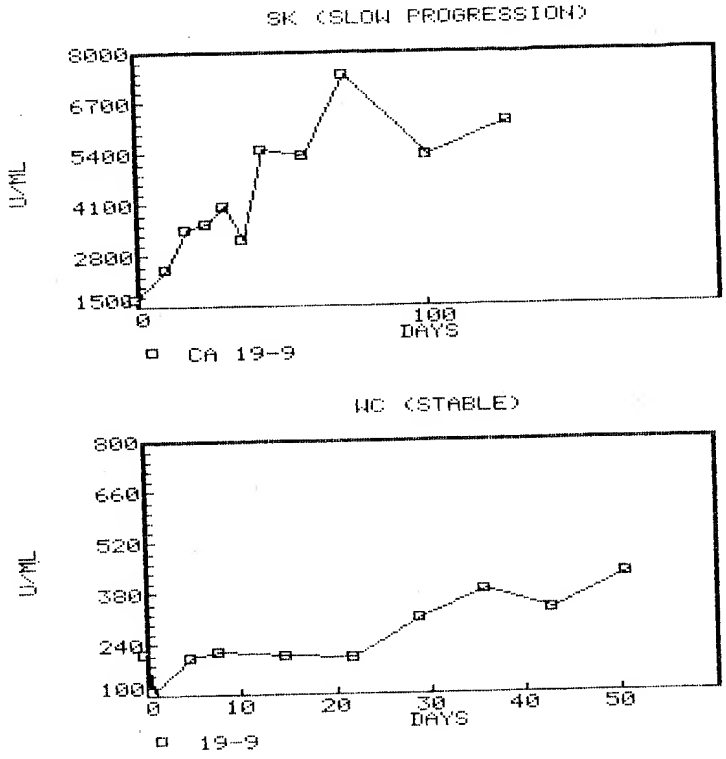

TABLE 1

DISTRIBUTION OF PATIENTS BY PRIMARY AND METASTATIC SITE

#	PRIMARY SITE	METASTATIC SITE
10	COLON	LIVER
2	COLON	+NODES
1	COLON	PELVIS
1	COLON	LUNG
1	COLON	VAGINA
2	COLON	SKIN
1	PANCREAS	NONE
3	PANCREAS	LIVER
1	STOMACH	+NODES

TABLE 2

LAB DATA

PT	THERAPY DATE	PRE 19-9	PRE CEA	LAST 19-9	LAST CEA	17-1A	73-3	TIME IN DAYS
SK	08/30/85	1719	323	6231	2038	1+/100%	1+/100%	130
RT	09/09/85	1716	135	1551	106	1+/100%	3+/30%	155
RM	09/17/85	16	0	62	2	NEG	1+/100%	141
MC	09/19/85	27	0	80	11	1+/50%	2+/100%	35
ML	09/24/85	56	3	39	4	1+/20%	2+/100%	138
LH	10/03/85	588	10	2485	23	NEG	1+/100%	96
HM	10/04/85	119	25	539	201	3+/95%	2+/75%	48
AK	10/10/85	231	259	550	1282	2+/100%	2+/100%	144
FD	10/21/85	10908	119	88088	308	NEG	3+/60%	56
FL	11/08/85	495	42	1133	28	1+/80%	4+/100%	26
RW	11/14/85	<5	1	8	1	2+/95%	NEG	54
RC	11/18/85	22	2	31	2	1+/100%	2+/80%	54
JS	11/21/85	4488	3	5049	4	+/5%	1+/50%	41
RS	11/26/85	1764	403	3465	1058	1+/100%	+/20%	80
RD	12/20/85	363	752	539	1210	1+/100%	2+/100%	40
JG	12/30/85	172	1	1386	4	NEG	1+/100%	38
WC	01/09/86	216	81	432	207	NEG	1+/95%	51
WH	01/16/86	8	1	<5	2	NEG	1+/95%	40
TD	01/22/86	14	1	-	-	1+/100%	1+/90%	--
EW	02/04/86	682	29	-	-	1+/10%	1+/100%	--
JL	02/12/86	<5	1	-	-	2+/100%	1+/100%	--
JC	02/19/86	957	241	-	-	1+/20%	2+/30%	--

Table 3

PT	AGE	PRIMARY SITE	METASTATIC SITE	PRE 19-9	PRE CEA
SK	68	COLON	LIVER	1719	323
RT	67	COLON	LIVER	1716	135
RM	63	PANCREAS	NONE	16	0
MC	69	COLON	+NODES	27	0
ML	67	COLON	+NODES	56	3
LH	62	STOMACH	+NODES	588	10
HM	59	COLON	PELVIS	119	25
AK	70	COLON	LIVER	231	259
FD	55	COLON	LIVER	10908	119
FL	71	COLON	LIVER	495	42
RW	49	COLON	LUNG	<5	1
RC	54	PANCREAS	LIVER	22	2
JS	61	PANCREAS	LIVER	4488	3
RS	53	COLON	LIVER	1764	403
RD	64	COLON	LIVER	363	752
JG	71	PANCREAS	LIVER	172	1
WC	60	COLON	LIVER	216	81
WH	59	COLON	LIVER	8	1
TD	73	COLON	VAGINA	14	1
EW	53	COLON	LIVER	682	29
JL	47	COLON	SKIN	0	1
JC	64	COLON	LIVER	216	81

Normal 19-9 is 0-37 u/ml
Normal CEA is 0-5 ng/ml

PT	AGE	SEX	TU DX
SK	68	F	1
RT	67	M	0
RM	63	M	1
MC	69	M	0
ML	67	M	0
LH	62	M	0
HM	59	F	0
AK	70	F	1
FD	55	M	1
FL	71	M	0
RW	49	M	0
RC	54	M	0
JS	61	M	0
RS	53	F	1
RD	64	M	0
JG	71	M	1
WC	60	M	0
WH	59	M	0
TD	73	F	0
EW	53	M	1
JL	47	F	0
JC	64	M	0

S - Stable
SP - Slow progression
D - Death
TE - Too early

INITIALS	PERFC BEFORI
MC	25%
FD	10(
FL	85%
JS	50%

17-1A	73-3	TIME IN DAYS
1+/100%	1+/100%	130
1+/100%	3+/30%	155
NEG	1+/100%	141
1+/50%	2+/100%	35
1+/20%	2+/100%	138
NEG	1+/100%	96
3+/95%	2+/75%	48
2+/100%	2+/100%	144
NEG	3+/60%	56
1+/80%	4+/100%	26
2+/95%	NEG	54
1+/100%	2+/80%	54
+/5%	1+/50%	41
L+/100%	+/20%	80
L+/100%	2+/100%	40
NEG	1+/100%	38
NEG	1+/95%	51
NEG	1+/95%	40
.+/100%	1+/90%	--
.+/10%	1+/100%	--
:+/100%	1+/100%	--
+/20%	2+/30%	--

PRE 19-9	PRE CEA
1719	323
1716	135
16	0
27	0
56	3
588	10
119	25
231	259
10908	119
495	42
<5	1
22	2
4488	3
1764	403
363	752
172	1
216	81
8	1
14	1
682	29
0	1
216	81

TABLE 4

CLINICAL DATA

PT	AGE	SEX	TUMOR DX DATE	17-1A TRT DATE	CLIN RESP	PREVIOUS THERAPY
SK	68	F	12/83	08/30/85	SP	CHEMO
RT	67	M	04/82	09/09/85	S	CHEMO, RAD
RM	63	M	11/84	09/17/85	S	NONE
MC	69	M	04/85	09/19/85	D	NONE
ML	67	M	07/83	09/24/85	S	IMMUNO
LH	62	M	04/85	10/03/85	SP	RAD
HM	59	F	06/84	10/04/85	S	RAD
AK	70	F	12/83	10/10/85	S	CHEMO
FD	55	M	11/83	10/21/85	D	CHEMO
FL	71	M	01/85	11/08/85	D	CHEMO
RW	49	M	02/85	11/14/85	S	NONE
RC	54	M	03/85	11/18/85	S	CHEMO, RAD
JS	61	M	08/85	11/21/85	D	NONE
RS	53	F	11/85	11/26/85	S	NONE
RD	64	M	07/85	12/20/85	SP	NONE
JG	71	M	10/85	12/30/85	SP	CHEMO, RAD
WC	60	M	04/85	01/09/86	S	RAD
WH	59	M	08/85	01/16/86	S	CHEMO
TD	73	F	05/85	01/22/86	TE	RAD
EW	53	M	12/84	02/04/86	TE	CHEMO, RAD
JL	47	F	02/85	02/12/86	TE	CHEMO, RAD
JC	64	M	09/85	02/19/86	TE	NONE

S - Stable
SP - Slow progression
D - Death
TE - Too early

TABLE 5

EXPIRED PATIENTS

INITIALS	PERFORMANCE BEFORE THERAPY	THERAPY DATE	EXPIRY DATE
MC	25%	09/19/85	11/02/85
FD	100%	10/21/86	01/03/85
FL	85%	11/08/85	12/11/85
JS	50%	11/21/85	12/14/85

TABLE 6

CA 19-9 vs CLINICAL RESPONSE

PT	% CHANGE in CA 19-9	# OF DAYS FOLLOWED	CLINICAL RESPONSE
SK	+ 262	185	SP
RT	NS	155	S
RM	+ 288	141	S
MC	+ 196	35	D
ML	− 10	138	S
LH	+ 323	96	SP
HM	+ 353	48	S
AK	+ 138	144	S
FD	+ 707	56	D
FL	+ 129	26	D
RW	*	54	S
RC	+ 41	54	S
JS	+ 13	41	D
RS	+ 96	80	S
RD	+ 48	40	SP
JG	+ 706	38	SP
WC	+ 100	51	S
WH	*	40	S
TD	TE	30	TE
EW	TE	28	TE
JL	TE	25	TE
JC	TE	20	TE

S - stable
SP - slow progression
D - death
TE - too early
NS - not significant
* - all 19-9 remain normal

ONSE

CLINICAL RESPONSE
SP
S
S
D
S
SP
S
S
D
D
S
S
D
S
SP
SP
S
S
TE
TE
TE
TE

TABLE 7

ANTI-IDIOTYPIC RESPONSE

INITIALS	THERAPY DATE	ANTI-ID RESPONSE	CLINICAL RESPONSE	DAY ANTI-ID TESTED
SK	08/30/85	+	SP	+45
RT	09/09/85	+	S	+38
RM	09/17/85	+	S	+40
MC	09/19/85	-	D	+35
ML	09/24/85	- (*)	S	+30
LH	10/03/85	-	SP	+26
HM	10/04/85	+	S	+18
AK	10/10/85	+	S	+18

S - Stable
SP - Slow progression
D - Death
* - To date the only anti-id data available is from 30 days post treatment. It is possible that later sera may have a positive anti-idiotypic response. This patient continues to be stable 138 days post treatment.

REFERENCES

1. Sears, Henry F., Herlyn, D., Steplewski, Z., and Koprowski, H. Effect of Monoclonal Antibody Immunotherapy on Patients with Gastrointestinal Adenocarcinoma. Journal of Biological Response Modifers 3:138-150, 1984.
2. Steplewski, Z, Herlyn D., Maul G., et al. Hypothesis: macrophages as effector cells for human tumor destruction mediated by monoclonal antibody. Hybridoma 2:1-5 1983.
3. Sears HF, Atkinson BF, Mattis J, et al. Phase-I clinical trial of monoclonal antibody in treatment of gastrointestinal tumors. Lancet 1982; 1:762-5.